Review: The Current Relevance and Use of Prednisone in Rheumatoid Arthritis

Key Words

Prednisone – pharmacodynamics – pharmacokinetics – glucocorticoid receptor – DMARD – modified-release prednisone – low-dose treatment – safety concerns

Summary

Prednisone is an old and very valuable drug in clinical use for over 60 years by now. It is well known by physicians and widely used for different kinds of inflammatory states including rheumatoid arthritis (RA). Clinical trials during the last 20 years have changed its clinical use, particularly with regards to dosage. Today, rheumatologists are treating their patients much more likely over a long period of time using a low-dose scheme. The effectiveness and safety of this low-dose use is the objective of the current clinical research and shall be enlightened in this drug profile.

It is also featuring current knowledge about the value of modified-release prednisone with regards to the just published results of the 2nd CAPRA (Circadian Administration of Prednisone in Rheumatoid Arthritis) trial. Moreover, the mechanisms of action of prednisone and its relatives will be summed up.

Introduction

Epidemiology

Rheumatoid arthritis (RA) is an autoimmune disease and the most frequent inflammatory arthritis. The latest data are showing an incidence of approx. 41 cases per 100.000 people a year; it appears to be rising with age and peaks among people between 65 and 74 years with rates up to 89 per 100.000 [1]. Studies show a prevalence of 0.5-1 % in the general population [2] while the lifetime risk of developing RA was estimated 3.6 % for women and 1.7 % for men, respectively [3].

Clinic

Though patients are typically suffering from symmetrical synovitis with joint pain, swelling and morning stiffness, RA is a disease with a systemic character, possibly leading to a variety of extra articular manifestations including vasculitis, serositis or even interstitial lung disease. Besides these more severe but fortunately less

frequent problems, constitutional symptoms like chronic disease's anaemia, weight loss or fatigue occur regularly, influencing the patient's quality of life negatively.

Pathogenesis

The underlying pathogenic mechanisms are complex and not yet fully understood. For further considerations it is helpful to distinguish between the effector cytokine levels and its causes. Among Rheumatologists and Immunologists it is common sense, that the symptoms of RA are strongly related to elevated pro-inflammatory cytokines within both, serum and synovia. Important actors here are Tumour Necrosis Factor (TNF)-α, but also Interleukin (IL-) 6 and maybe IL-17A. This general assumption is supported by studies showing elevated cytokine levels in RA patients as well as the very successful clinical use of drugs inhibiting those proteins directly (e.g. TNFα-blocking agents) or rather indirectly (e.g. glucocorticoids).

On the contrary, the riddle of the actual cause of this disturbed cytokine patterns is not satisfactorily solved yet. Different kinds of leukocytes seem to be involved, including T cells and monocytes.

Of great interest here are monocytes which can differentiate into macrophages and migrate to the synovial membrane, where they are found in increased frequencies and are considered to take part in the typical tissue damage after getting activated by cytokines, T cells or via receptors like the TLR. Radiologic articular destruction seems to be positively correlated with the amount of tissue infiltration by macrophages [4].

Moreover, most inflammatory cytokines, which are important in RA and which decrease in response to conventional therapy using anti-inflammatory drugs (such as GCs) as well as directly acting anti-cytokine therapies (e.g. TNFα inhibiting agents), are mainly produced by those cells. This is particularly true for TNFα, making them to one major mediator of inflammation together with other cells being involved in the activation process as well [5, 6]. Anti-cytokine therapy is therefore always an anti-monocyte therapy, too. This assumption is emphasized by the recent findings about reverse signalling through the transmembrane TNF: as we were able to show, Infliximab-ligation of tmTNF on monocytes leads to inhibition of the constitutive NF-κB activation, suppresses spontaneous IL-1β production and induces apoptosis within monocytes in RA patients but not in healthy controls [7]. There is also

evidence, that the monocyte cell set in RA is disturbed with patients having expanded pathological subsets at the expense of classical monocytes [8, 9].

This paper is not aiming to deliver a detailed description of the assumed pathogenic process leading to RA though. The typical problems RA patients are suffering from are the clinical tip of the iceberg: a synovial inflammation caused by cytokines and other enzymes as a result of a complicated, probably autoimmune process.

Rapid symptom relieve due to compromising the autoimmune reaction within the joint is one of the most important glucocorticoid action, in particular if used in high doses. A more detailed view on the mechanism of action and recent clinical trials will be provided later in this article.

Diagnosis

Today's diagnosis of RA is based on the classification criteria of the American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR) published in revised form in 2010 [10]. They were created as a score-based algorithm and consist of 4 categories *(Table 1)*. An overall score of ≥ 6/10 is needed for classification of a patient as having a rheumatoid arthritis. These criteria should only be used if an RA is likely, i.e. the patient should have at least one joint with a definite clinical synovitis, which is not any better explained by another disease.

The sensitivity of these criteria was measured recently to be higher than its precursors' from 1987 while having a lower specifity [11]. A clinically wide use of those current criteria is one of the reasons for a different clinical presentation of RA resulting in an earlier diagnosis with much less radiological joint alterations.

TABLE 1. ACR/EULAR classification criteria for rheumatoid arthritis (2010) [10]

A.	Joint involvement	
	1 large joint	0
	2-10 large joints	1
	1-3 small joints	2
	4-10 small joints	3
	> 10 joints (at least 1 small joint)	5
B.	Serology	
	Negative RF *and* negative ACPA	0
	Low-pos. RF *or* low-pos. ACPA	2
	High-pos. RF *or* high-pos. ACPA	3

C.	Acute-phase reactants (at least one test result is needed)	
	Normal CRP *and* normal ESR	0
	Abnormal CRP *or* abnormal ESR	1
D.	Duration of symptoms	
	< 6 weeks	0
	≥ 6 weeks	1

Therapy

Glucocorticoids (GC) have been the cornerstone of RA's therapy for decades and are still invaluable, despite disease-modifying antirheumatic drugs (DMARDs) like methotrexate as the backbone of the non-biological therapy and modern biologics such as Tumour Necrosis Factor (TNF)-α inhibiting agents. This is especially true when talking about acute disease flares where a rapid symptom-releasing effect is needed. Furthermore, GCs are very valuable therapeutics in bridging the time until the chosen DMARD takes full effect.

The focus of this review will be on prednisone, a prototype GC, widely used by physicians all over the world. Its clinical importance is emphasized by the fact that the potency of other GCs is often compared to prednisone, being termed "prednisone equivalent" when prescribing or advising the use of a GC. *Table 2* gives an overview about different GCs and their distinct half-lives as well as duration of action.

TABLE 2. Glucocorticoid comparison chart [12]

	Glucocorticoid	*Relative Potency*	*Equivalent dose (mg)*	*Plasma half-life (min)*	*Biological half-life (hrs)*
Short acting	Hydrocortisone	1	20	90	8-12
	Cortisone	0.8	25	30	8-12
Intermediate acting	Prednisone	4	5	60	12-36
	Prednisolone	4	5	200	12-36
	Triamcinolone	5	4	300	12-36
	Methylprednisolone	5	4	180	12-36
Long acting	Dexamethasone	25-30	0.75	200	36-54

Overview

GCs are the most commonly used immunosuppressive drugs today. Moreover, they probably represent one of the most important and frequently used drug classes at all, finding their place in almost any medical discipline. Most of the GC members are known since the first half of the 20th century, their positive effect for the use in RA was firstly described 1950 [13].

Clinical characteristics as well as the side effects are well known, making GCs safe drugs with a good benefit-risk ratio when used with reason. They are still irreplaceable in the therapy of rheumatoid arthritis: on the one hand they are important for induction therapy in an acute exacerbation; on the other hand their use in long-term therapy is underestimated.

There are plenty of generics from different manufacturers and it does not exist any competition at the moment. However, a modified-release (MR) prednisone was developed as a new drug formulation. Several studies were able to show a temporal relationship between RA symptoms and increased blood levels of pro-inflammatory cytokines such as interleukin 6 (IL-6), indicating a circadian rhythm for serum cytokine concentrations [14-18].

Having the knowledge about the proposed circadian rhythm of pro-inflammatory cytokines and the physiological cortisone release/tissue sensitivity in mind, Arvidson et al. made an important clinical observation: low-dose prednisone, administered at 2 a.m., leads to a significant decrease of pain, stiffness and serum IL-6 in the morning [19]. This finally eventuated in the idea of creating a modified prednisone with a time-delayed onset of action. The undertaken efforts resulted in a tablet formulation with a 4-hour-timed prednisone release after oral intake, giving the possibility to administer the drug at 10 p.m. and releasing prednisone at approx. 2 a.m. [20].

In this context, the specific timing of the medication, which is linked to the interaction between IL-6 and the hypothalamic-pituitary-adrenal (HPA) axis, may correct a postulated deficiency of HPA control in RA [21, 22].

Importantly, drug effects and dosage seem to be equivalent to prednisone. Clinical use, potency and safety of this ‘chronotherapy’ have been investigated in two trials, acronymed CAPRA (Circadian Administration of Prednisone in Rheumatoid Arthritis), published in 2008 [20] and 2013 [23]. MR prednisone was developed by Horizon Pharma and Skye Pharma and has been named LODOTRA®. It gained approval for

Europe in 2009 after the promising results of CAPRA-1 und is being commercialized and distributed by Mundipharma. In the U.S., it has been named RAYOS® and is distributed by the licensee himself since 2012 after approval of the FDA.

Chemistry

Prednisone ($C_{21}H_{26}O_5$) is a synthetic glucocorticoid and is derived from cortisone using microbiologically oxidation [24]. In the 1950s, it was named metacortandracin in the first place, regarding to its steroid hormone matrix. The only difference between endogenous cortisone and prednisone is the added double binding between C_1 and C_2 *(Figure 1)*, leading to an increase in anti-inflammatory potency of 4 to 5 times with less side effects [25]. Prednisone is inert and the precursor of prednisolone, making the latter one the active metabolite [26].

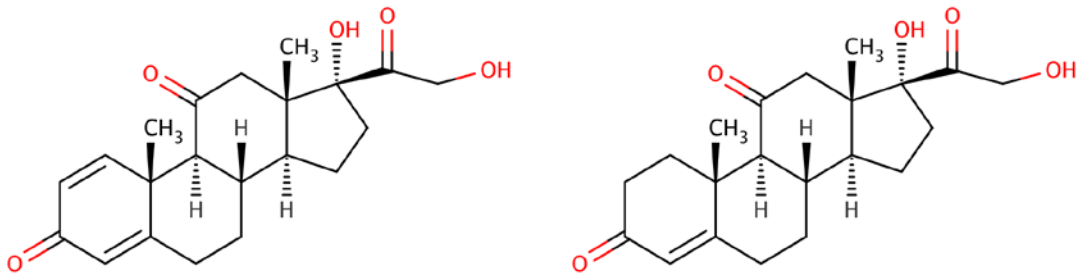

FIGURE 1: Prednisone (left) vs. cortisone (right). Note the double binding in prednisone between C_1 and C_2.

Carrying a high immunosuppressive potential, prednisone is used for the treatment of many autoimmune diseases as well as inflammatory states including allergic reactions. In higher doses it also has a place in oncology, in particular with regards to lymphomas.

Pharmacodynamics

GCs are immunosuppressive drugs, providing their effects on different ways and in a dose-dependent manner. They are widely used and very common in today's clinical practice. In general, GCs provide an inhibition of any inflammatory process, an effect, which seems to be dose-dependent. In order to describe their way of function further, one can distinguish long-term genomic from faster non-genomic effects.

Genomic effects

GCs provide most of their effects using the cytosolic glucocorticoid receptor (cGCR) being part of a multi-protein receptor complex, also consisting of heat shock proteins (Hsp) and several kinases [27, 28]. Since GCs are lipophilic, they are able to pass through the plasma membrane, reaching their distinct receptor within the cells. In this context, the 17-hydroxy, 21-carbon steroid configuration is the reason for the mentioned lipophilicity as well as a successive receptor binding [29]. These general characteristics are also applicable for prednisone and prednisolone. After GC's binding to the cGCR, the receptor-associated proteins dissociate and the complex of GC/cGCR translocates into the nucleus, binding as a homodimer to specific DNA binding sites (GC responsive elements) [27]. This action, termed transactivation, consecutively leads to the synthesis of anti-inflammatory proteins (e.g. lipocortin 1, IL-10) as well as regulatory proteins (probably important for metabolism and various GC side effects). Furthermore, GC/cGCR monomers are able to negatively interfere with transcription factors (termed transrepression) such as nuclear factor-κB (NF-κB), activator protein-1 (AP-1) and nuclear factor for activated T cells (NF-AT), subsequently reducing the expression of pro-inflammatory proteins like interleukin-1 (IL-1), IL-6 or tumour necrosis factor α (TNFα) [30, 31].

Decreasing TNFα, one of RA's major therapeutic target, probably leads to less joint erosions since TNFα physiologically induces the production of 'receptor activator of nuclear factor kappa B ligand' (RANKL). Among others, RANKL is supposed to be involved in joint erosions by activating osteoclasts [32].

In general, the two mechanisms, transrepression as well as transactivation, provide the anti-inflammatory effects of prednisone [33].

Non-genomic effects

Administrating prednisone or other GCs on any route, especially in high doses, often leads to a rapid clinical improvement, depending on the indication. Such an impact actually seems way too fast for being based on genomic-mediated effects. That observation led to the conclusion, that there must be other mechanisms of action since significant changes on cellular level take some time, ranging from hours to days. The assumption of the existence of non-genomic effects is emphasized by the fact, that all cGCR are occupied, when administering 100-200 mg prednisone a day; the effect of higher dosages, therefore, cannot be explained by being glucocorticoid receptor-mediated [34].

Proposed mechanisms for those non-genomic effects seem to be typically dose-dependent (above 30 mg prednisone-equivalent per day [35]) and are shown in *Table 3*.

TABLE 3. Rapid glucocorticoid-mediated effects

non-genomic effect	proposed molecular mechanism
Specific interaction with cytosolic (c)GCR	heat shock proteins [Hsp] (e.g. Hsp 90) and kinases of the MAPK pathway (e.g. Src) as part of the multi-receptor complex providing a non-genomic inhibition of arachidonic acid release [28, 36, 37]
Physiochemical interactions with cellular membranes	membrane bound proteins are functionally disturbed (resulting in a decreased transmembrane cation cycling) as well as the immune cell's energy supply is reduced due to uncoupling of oxidative phosphorylation (direct effects on the inner mitochondrial membrane resulting in proton leak); in total, the immune cell's function is compromised [38-42]
Specific interaction with membrane-bound (m)GCR	probably non-dose dependent, mGCR was firstly found on amphibian brains and recently discovered on human peripheral blood mononuclear cells (PBMCs); binding seems to provide non-genomic effects, mGCR expression is up regulated on monocytes by immunostimulation, possibly providing a negative feedback mechanism; further investigations on distinct function are needed [43-46]

Dosage

Genomic and non-genomic effects as mentioned above mediate the effects of prednisone. The impact provided by glucocorticoids is dose-dependent; this is true for both described mechanisms of action. Nonetheless, there are differences though.

While the genomic effects seem to have a ceiling effect on high doses (complete GCR saturation), the non-genomic effects still increase, providing an additional GC effect; hence, with raising the dose the desired overall effect increases [35]. However, the known side effects of GC are also strongly dose-dependent: the longer the therapy or the higher the dose, the more relevant the GC-side effects become, i.e. the more often they may occur [47].

Typical side effects such as hypertension, diabetes, osteoporosis, myopathy, increased body weight or redistribution of body fat partly result from the actual hormone effects as well as the remaining intrinsic mineral corticoid effect. Other undesirable effects include cataract, infections, skin alterations and depressions, just to name the most common ones [32, 48, 49].

Five dosage steps can be distinguished by doses in prednisone equivalent [35]:

I.	low-dose therapy	usually up to 7.5 mg a day
II.	medium-dose therapy	usually above 7.5 up to 30 mg a day
III.	high-dose therapy	usually above 30 up to 100 mg a day
IV.	very high-dose therapy	usually doses above 100 mg a day
V.	pulse therapy	usually ≥ 250 mg a day for a few days

As we will show later, low doses provide important effects on rheumatoid arthritis with moderate adverse events being comparable to placebo.

Pharmacokinetics & Metabolism

After taken orally, prednisone uptake is usually very fast through the intestine. Prednisone itself is inactive and needs to be converted into prednisolone by hydrogenation of the C_{11} ketone group *(Figure 2)* taking place predominantly within the liver [50]. The pre-conversion plasma half-life of prednisone is about 60 minutes; its biological half-life was estimated 12-36 hours [51, 52]. Prednisone and especially its metabolite prednisolone both show a high plasma protein binding of up to 95 % [50]. In this respect, binding is not only provided by albumin, but also by transcortin and is strictly dose-dependent. Its use in patients with a severe liver disease remains controversial due to a potentially reduced conversion to prednisolone, which though seems to be offset by the decreased prednisolone clearance [26]. If either

prednisone or prednisolone is used in the present of liver disease, the dose should be reduced accordingly [53].

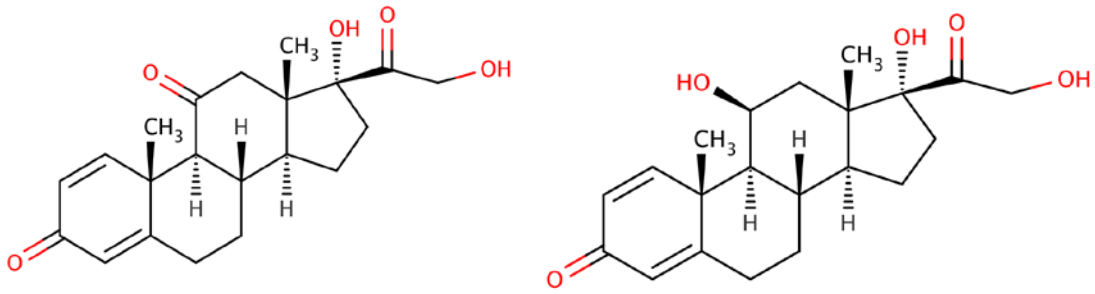

FIGURE 2: Prednisone (left) vs. prednisolone (right). Note the ketone group of prednisone in C_{11} being hydrogenated to form the active prednisolone.

Modified-release (MR) Prednisone

As mentioned in the introduction section of this paper, 'chronotherapy' by using modified-release prednisone is the latest innovation in clinical use of glucocorticoid treatment in RA. Two phase III clinical trials with the acronym CAPRA investigated that new drug formulation with different aims.

CAPRA-1 [20] compared MR prednisone to immediate-release prednisone, taken at bedtime and in the morning (6-8 a.m.), respectively. The study design was double-blind and randomized, using a double-dummy technique for blinding (application twice a day per patient). Prednisone dose ranged between 3 and 10 mg a day, depending on the previous medication.

Results showed a significant reduction of morning stiffness' duration favouring the MR prednisone group (main objective) to a clinically meaningful extent (mean absolute reduction 44 vs. 23 minutes). The mean relative treatment difference between the two groups was 22.4 % (p=.045), the mean absolute difference was 29.2 minutes (p=.072).

Secondary parameters like the Disease Activity Score (DAS) 28 or patient's global assessment of disease activity did not show any significant changes.

In addition, after having proven the efficacy of MR prednisone in comparison to its immediate-release competitor, *CAPRA-2* [23] was seeking for other aims. Focusing on using MR prednisone as a supportive therapy, added to an existing DMARD, the primary endpoint after 12 weeks was defined as assessing the percentage of patients

with a 20 % improvement of RA signs and symptoms (i.e. ACR20 response). Furthermore, changes in morning stiffness, pain and DAS28 were also evaluated. The trial was designed double-blind and placebo-controlled, the chosen dosage for MR prednisone was 5 mg a day.

The results showed better response rates in the DMARD plus MR prednisone group for both, ACR20 ($p<.001$) and ACR50 ($p<.006$). Moreover, the reduction in morning stiffness and fatigue reduction was found being significantly greater, as well as the improvements in physical function. Another finding was a higher amount of patients gaining DAS28 remission, without reaching significance, though.

A recent clinical trial revealed that switching from immediate release prednisone or 6M-prednisolone to low-dose prednisone significantly improved reported outcomes over 4 months in a large number (n=950) of RA patients [54].

Taking these findings into consideration, MR prednisone is a promising drug, already used in clinical practice in Europe for a few years by now. Patients can achieve important benefits especially with regards to their quality of life. With side effects [20, 23, 55] and pharmacokinetics [56] comparable to immediate-released prednisone, it is a valuable alternative to the conventional drug. The differences in the therapy costs are expected to be diminished in the upcoming years due to MR prednisone production by competitive manufacturers when the current patent protection expires. Furthermore, recent calculations from the UK show the cost-effectiveness of MR prednisone even today when considering the increase in quality-adjusted life years (QUALYs), resulting in an advantageous incremental cost-effectiveness ratio (ICER) below the cost-effectiveness threshold applied by the UK National Institute of Health and Clinical Excellence (NICE) [57]. Moreover, MR prednisone can delay the start of an expensive biologic treatment, potentially saving costs to a considerable extent [58].

Long-term low-dose prednisone in rheumatoid arthritis

Just as with many other drugs, efficacy of prednisone depends on different factors; one of them being the dosage utilised with higher doses exhibiting increasing effects. When looking back on the last few years, there has been a lot of discussion among rheumatologists about the usefulness of low dose prednisone. Today, low-dosed therapy is commonly used, especially in combination with a potent DMARD such as MTX. After the clinical observation of positive effects of GC, various trials have been

conducted to evaluate the actual effectiveness in (early) RA scientifically. Those trials (*Table 4*) have been designed differently; some of them aiming to prove the mere effectiveness [59-61], others aiming to prove the impact on radiographic joint destruction in terms of slowing down progression [60, 62-65].

The Utrecht study, originating over 10 years ago in 2002, and its follow-up (2006) showed a clinical benefit of 10 mg prednisone monotherapy with inhibiting radiographic joint destruction which even remained in the 3-year follow-up period after discontinuing prednisone having been taken for 2 years in the original study [65, 66].

In contrast, Svensson and colleagues [63] investigated a combination therapy with adding 7.5 mg of prednisone to an initial DMARD. This scheme retarded the radiographic progression of joint destruction after 2 years and was also associated with a higher remission rate compared to placebo. The gained remissions after 2 years were also associated with less radiographic damage being still present after 2 years in the follow-up period [62].

Wassenberg [67] and Bakker [64] also investigated prednisone as an additional therapy to an existing DMARD and came to similar results in their clinical trials also demonstrating less joint destruction as well as faster clinical responses in terms of clinical response, e.g. ACR70. Bakker et al used 10 mg of prednisone, which slightly exceeds the definition of a low-dose therapy without having significant more adverse events in the prednisone group compared to the placebo group. Montecucco [60] conducted a trial focusing on the effect of prednisone added to an existing MTX therapy. Evaluating the impact of this combination on remission rates and synovitis, they were able to demonstrate higher clinical remission rates and less frequent subclinical synovitis measured by ultrasound. The mean DAS28-difference between the prednisone and placebo group at the end of the study was not significant (just as seen in the trial by Bakker et al), but initially (i.e. 2-6 months) the DAS28 fell much more rapidly reaching significance.

The mere effectiveness of low-dose prednisone was proven by Pincus et al [59] when conducting a trial having withdrawal from the study due to patient-reported lack of efficacy as its primary endpoint. All participants have been on low-dose prednisone before baseline and were randomized either to a prednisone-continuing arm or to placebo. Significantly more patients withdrew from the placebo group during the study duration.

Den Uyl et al [61] compared a low dose-prednisone scheme (7.5 mg per day) after an induction therapy using initial doses of 60 mg and 30 mg, respectively. The results demonstrate that the reduced induction therapy is not inferior to the higher dose with regards to a comparable low DAS44 < 1.6 in both groups.

When summing up those results (see *Table 4*), a low-dose prednisone therapy seems to be helpful in terms of inducing a remission and, more important from the long-term point of view, in reducing the radiographic measurable joint damage when used over a long period (2-4 years), even after discontinuing the therapy. According to the literature, a possible persistence of this effect in a prolonged use exceeding 4 years was not examined so far. So far studies addressing the question of a prolonged effect after more than 4 years are missing. However, clinical trials for such a long period are rather difficult to realise, but are nevertheless warranted.

The long-term use of GCs beyond an induction or “bridging” purpose is very common in clinical practice: of over 4.300 RA patients at 48 sites in 15 countries 66 % were found to be taking GCs [68]. They are used for combination therapy with standard DMARDS such as MTX as well as a concomitant medication for biologic agents. Some questions still remain unanswered yet, e.g. how to handle the GCs after tapering down the biologic agent when the patient gains remission [69].

In general, DMARDS are defined as drugs for use against rheumatoid arthritis going beyond symptom release but having an influence on the long-term prognosis of the disease (especially with regards to disability) [70, 71]. More precisely, we are talking about joint damage and quality of life. Having the reduced radiographic progression in mind, one must conclude, that an additional low-dose prednisone therapy is meeting the criteria of a DMARD, putting that drug in a whole new perspective.

Its additional use provides great benefits in terms of modifying the disease regarding to less joint destruction and inducing remission more rapid.

In most of the RCTs discussed in the review at hand, adverse events have been recorded and analysed, mainly showing comparable side effects between low dose-prednisone therapy and placebo. Therefore, one can conclude that low-dose prednisone in early RA is an effective, promising and cost-efficient therapy, especially in combination with established DMARDS such as MTX [72, 73]. It seems to be superior to a DMARD monotherapy and could be able to retard radiologic joint destruction as well as the expensive competing biological-DMARD combination. Furthermore, GC may be able to prolong the survival time of conventional DMARDs

leading to a better effectiveness and/or reduced side effects of various DMARDs [74]. Besides, there is little evidence for severe side effects deriving from that low-dosed GC therapy.

Side effects and safety

The use of prednisone, especially the low-dosed use in the long-term, was shown to be safe with modest adverse effects and without significant toxicity. These conclusions are based on clinical trials with prednisone/prednisolone in low-dose use. Those trials have been extensively reviewed, among others, da Silva [75, 76] and Hwang [77] both wrote excellent papers on that topic. A meta-analysis of Hoes et al [78] shows a low to moderate risk for adverse events when using prednisone in a low-dose scheme for treating RA.

Newer clinical trials, published within the last years do not change that view on GCs in practical use. As named above (*see pharmacodynamics*), a low-dose prednisone therapy is actually defined as doses up to 7.5 mg/d prednisone equivalent.

The already mentioned trial of Bakker et al [64], consisting of 236 patients being on MTX therapy with 117 patients taking additionally 10 mg of prednisone reported adverse event-rates comparable between the prednisone and placebo group (74 vs. 79 %). Furthermore, withdrawal rates due to AEs have not been significantly different (14 vs. 17 %), even favouring the prednisone group. Montecucco et al [60] only provided limited data on AEs. Obviously, AEs due to prednisone did not lead to any withdrawal, while AEs contributed to MTX led to discontinuation in 10 patients from the MTX-only group while 6 patients from the MTX plus prednisone group withdrew. This difference was not significant though but underlines the assumption of a low to moderate risk when using low-dosed glucocorticoids over a longer time (1 year and above).

Comparable results demonstrated Svensson et al in their BARFOT study [63] with most withdrawal being contributed to the DMARD. Overall, 26 patients from the prednisone group and 24 from the MTX-only arm discontinued; only 5 withdrawals were related to prednisone (diabetes, proteinuria, stria, weight gain, cushingoid features) with 110 from the original 119 patients randomized to the prednisone arm persisting through the whole study. From even more interest though is the finding, that there was no significant difference in bone loss between the patients taking prednisone over a period of 2 years and those who did not. Bone mineral density

(BMD) was measured using dual x-ray absorptiometry (DXA) at the lumbar spine and the femoral neck.

Osteoporosis

The authors further investigated the BARFOT population, measuring markers of bone metabolism being responsible for bone formation and degradation, respectively [79]. They again performed DXA at the mentioned locations. While BMD in the spine decreased in both groups (though significantly more in postmenopausal women), BMD in the femur decreased in the placebo group only. Another finding was a positive correlation between pro-inflammatory markers/cytokines such as CRP or IL-6 and the bone resorption markers. Consequently, the investigators concluded that a low-dose prednisone therapy could be able to counteract the negative impact of the RA-mediated inflammation on the femoral bone tissue. This influence of RA on the bone metabolism has already been described before [80]. The rather negative effect of prednisone on the lumbar spine on the other hand could be explained by the dual impact of prednisone and the postmenopausal status of those patients on bone synthesis.

These findings are empowered by a recent study, also investigating the influence of a low-dose prednisone therapy (5-7.5 mg) vs. placebo over 2 years on BMD and body fat. The trial consisted of 50 patients in each arm and brought up no association between prednisone therapy and BMD, though the body fat mass in the prednisone group increased significantly [81].

As a consequence, supplemental prescription of calcium and vitamin D is recommended by the EULAR only for prednisone doses of 7.5 mg and more [82, 83]. This recommendation probably derives from the observations of RA itself interfering with bone metabolism [80, 84] and the growing evidence of prednisone counteracting that negative inflaming impact, especially in early RA and low-dose use [79, 81].

Cardiovascular side effects

Typical cardiovascular side effects of GCs are hypertension, dyslipidaemia and atherosclerosis. Retrospective studies show an increased risk of cardiovascular events in RF-positive RA patients after being exposed to GCs, in particular when being positive for rheumatoid factor (RF) [85]. This observation is supported by the finding, that a lower DAS28 in RA patients seems to be associated with a lower blood

pressure, further emphasizing the importance of the underlying inflammatory disease activity for cardiovascular changes [86].

While a therapy using prednisone, especially in higher doses and over a longer period of time, is associated with accelerated arteriosclerosis and undesired changes in the blood lipid profile [87], newer investigations on a low-dose therapy in RA show rather positive impacts on the blood lipid profile such as elevated levels of HDL [88-91]. Furthermore, low-dose prednisone therapy neither seems to be associated with heart failure nor increases the risk of developing hypertension [65, 67, 92]. No impact on atherosclerosis could be shown in the BARFOT study population; neither intima-media thickness of the carotid arteries nor the prevalence of atherosclerotic plaques or the endothelial function differed between the control group and the patients being treated with prednisone for up to 5 years [93]. It needs to be mentioned here that elevated cholesterol levels have been found though. Fortunately, serious cardiovascular events such as myocardial infarction are rather rare events (0-1 events/100 patient years for glucocorticoid-using patients) [83].

Type II Diabetes Mellitus

Glucocorticoids are well known to cause insulin resistance and therefore induce diabetes mellitus especially when administrated in medium or high doses. The influence of a low-dose prednisone therapy on peripheral insulin resistance and blood glucose levels is difficult to evaluate.

Most available data derives from clinical trials on the effectiveness of low-dose prednisone, only noting the mere blood glucose levels. Summing up the provided results, there is no evidence of a correlation between low-dose prednisone therapy and developing a new type II diabetes [63-65, 67, 93]; a progression from an existing glucose intolerance to a manifest diabetes mellitus is thought to be much more likely [94, 95]. These assumptions are supported by the findings of a recent study by Hoes et al [96]: the authors investigated the glucose metabolism in RA patients with and without GC therapy, compared to healthy controls. They were able to demonstrate inflammatory RA disease activity itself was being associated with disturbed glucose metabolism, insulin resistance and impaired β-cell function, independent of GC therapy. The cumulative GC dose though also seemed to have an independent negative impact on insulin sensitivity and glucose tolerance. However, the latter association decreased when being corrected for the current disease activity [96] and

might be confounded by indication in terms of longer disease activity (i.e. higher cumulative dose), which is able to influence glucose metabolism as mentioned above.

Infections

Due to the immunosuppressive effects of glucocorticoids, GC therapy usually is associated with an increased risk of developing even severe infections. The results regarding infections under low-dose GC gained from clinical trials and literature reviews are conflicting. An older meta-analysis from 1989, reviewing 71 controlled clinical trials with different GC-indication did not find an increased risk for infections when using daily doses of less than 10 mg of prednisone (cumulative dose below 700 mg) [97]. Almost in line with these findings, a newer review from 2010 including 15 trials regarding to low-dose use of GCs in RA, only found an “poorly” increased risk of infections for low-dose prednisone use [98]. It needs to be mentioned that the authors are criticizing the rather insufficient data, strongly recommending further studies on that topic. A more recent nested control-case study from Australia with over 16.000 patients shows a dose dependent increased relative risk of common non-serious infections in RA patients aged over 65 years (mean age: 70.9 years). The RR was calculated 1.10 for doses of ≤ 5 mg/d of prednisone in contrast to 1.85 for doses above 20 mg/d of prednisone. The adjusted RR for all prednisone doses was 1.20 [99]. These findings go along with another big retrospective study by Widdifield et al [100], who again found an elevated risk for getting serious infections including bacterial pneumonia, herpes zoster and skin infections in elder RA patients (mean age: 72.4 years); odds ratios were calculated in this study from 3.96 (low doses) to 7.57 (high doses).

The German biologics register RABBIT also shows a dose-dependent increased risk for serious infections under GC treatment [101].

In contrast, the recent clinical trial by Bakker and colleagues [64] again was unable to find a significant difference in the occurrence of infections between RA patients taking prednisone and patients who did not. The mean age here was 54 years in the prednisone group and 53 in the placebo group, respectively.

In summary, the risk of developing an infection seems to be slightly increased when being on a low-dose prednisone therapy to treat rheumatoid arthritis. This risk might be further increased though by the patient’s age. Since RCTs are unable to detect an

increased risk for developing infections while retrospective data is suggesting the opposite, there might be a connection to RA and inflammatory activity itself.

Glaucoma

GC-administration goes along with an increased risk of developing ocular hypertension; this risk though seems dose-dependent with odds ratios of 1.26 (less than 40 mg/d of hydrocortisone) up to 1.88 (80 mg/d of hydrocortisone and more) [102]. Recent data on that topic is missing, making the importance of glaucoma in low-dose prednisone therapy uncertain. Following the EULAR guidelines is therefore recommended [82, 83]. Patients should be referred to an ophthalmologist for glaucoma screening if diabetes is present, the family history is positive for glaucomas or they are suffering from a high myopia.

What side effects are most important according to patients and their treating rheumatologists though? Van der Goes et al asked 140 patients and 110 rheumatologists about “the most worrisome adverse events”. While osteoporosis, diabetes and cardiovascular diseases were ranked within the five most worrisome AEs on both sides, the five most worrisome AEs got 50 % of the total scores among rheumatologists compared to only 35 % in the patients group [103]. This result emphasizes how the patients are recognizing the possibility of all side effects while physicians are more concerned about the rather life threatening ones.

Summing up the results from the current literature (see above and *Table 4*) as well as our own clinical observations, low-dose prednisone therapy is associated with some mild to moderate toxicity, which might be overestimated by physicians using the drug. Low-dose use of prednisone provides great clinical benefit with the potential of a disease-modifying therapy due to the positive impact on radiographic progression of joint destruction. Trials with a low-dose therapy for a limited period of time (up to two years) show comparable amounts of AEs between the control group and the prednisone group. Definite conclusions in terms of low-dose GC safety are difficult to draw since distinct safety trials and sufficient safety data from clinical trials are lacking. This problem has already been addressed by the current EULAR guidelines on GC-use in rheumatic diseases [82].

There exists convincing evidence though that low-dose use of prednisone is a promising option for early RA patients which can be considered as a safe and potent drug when used thoughtful by an experienced physician under proper monitoring,

having the patients co-morbidities and the individual risk for distinct side effects in mind.

Low-dose Prednisone

TABLE 4. Results of recent prospective, randomized, placebo-controlled clinical trials on the low-dose use of prednisone

1st author	den Uyl [61]	Bakker [64]	Montecucco [60]	Hafström [62]	Pincus [59]	Wassenberg [67]	Svensson [63]
published	2013	2012	2012	2009	2009	2005	2005
n (P vs. nP)	81 vs. 83	117 vs. 119	110 vs. 110	64 vs. 86	15 vs. 16	94 vs. 98	119 vs. 131
RA diagnose	≤ 2 years	< 1 year	< 1 year	< 1 year	any	< 2 years	< 1 year
duration	4 months	2 years	1 year	2 (4) years	(12) 24 weeks	2 years	2 years
Prednisone dose	30 vs 60 mg induction dose, tapered down	10 mg	6.25 mg	7.5 mg	1-4 mg	5 mg	7.5 mg
DMARD & dose	MTX 10-25 mg qwk SSZ 1000/2000 mg	MTX 10 mg qwk	MTX 10 mg qwk	any	any	any	any
remarkable outcome	lower-dosed GC-induction therapy is not inferior	less radiographic joint destruction	clinical & US remission	remission, less radiographic joint destruction	efficacy proven by withdrawal (placebo)	less radiographic joint destruction	less radiographic joint destruction
ACR20	72 vs. 74 % (n.s.)	65 vs. 61 % (n.s.)	n.a.	n.a.	n.a.	n.a.	n.a.
ACR50	62 vs. 57 % (n.s.)	53 vs. 42 % (n.s.)	n.a.	n.a.	n.a.	n.a.	n.a.
ACR70	49 vs. 38 % (n.s.)	38 vs. 19 % (p=.002)	n.a.	n.a.	n.a.	n.a.	n.a.
DAS28[1]	n.a.	0.26 (n.s.)	0.27 (n.s.)	n.a.	n.s.	n.a.	0.8 (p=.02)
DAS44[1]	n.s.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
VAS[1]	n.a.	n.a.	8.8 (p=.04)	n.a.	n.a.	n.s.	n.a.
remission[2], minimal disease activity[3]	41 vs. 49 % (n.s.)[3]	n.a.	44.8 vs. 27.8 % (p=.02)	55 vs. 30 % (p=.003)	n.a.	n.a.	55.5 vs. 32.8 % (p=.0005)
Ratingen Score[4]	n.a.	n.a.	n.a.	n.a.	n.a.	3.14 (p=.006)	n.a.
combined SHS[4]	n.a.	n.a.	n.a.	n.s.	n.a.	7.20 (p=.022)	n.a.
change in SHS[5]	n.a.	n.s.	n.a.	n.a.	n.a.	n.a.	1.8 vs. 3.5 (p=.019)
combined SHS remission[6]	n.a.	n.a.	n.a.	7.5 vs. 13.5 (p=.009)	n.a.	n.a.	3.0 vs. 8.0 (p=.005)
PD neg.[7]	n.a.	n.a.	69.8 vs. 53.3 % (p=.04)	n.a.	n.a.	n.a.	n.a.
AEs	94 vs. 90 % (n.s.)	74 vs. 79 % (n.s.)	11 vs. 9 % (n.s.)	n.a.	no meaningful AEs	71 vs. 74 % (n.s.)	22 vs. 18 % (n.s.)
withdrawal	n.a.	n.a.	n.a.	n.a.	3 vs. 11 (p=.021)	n.a.	n.a.

[1] mean difference at the end of trial

[2] frequency of patients (P vs. nP) reaching remission, defined as DAS28 < 2.6

[3] minimal disease activity, defined as DAS44 < 1.6

[4] mean difference between P and nP at the end of trial

[5] median change in SHS between P and nP compared to baseline at the end of trial

[6] median SHS in all patients reaching remission (remission vs. non-remission)

[7] Power Doppler-negativity, P vs. nP[7] patients withdrawn from study due to lack of efficacy (P vs. nP)

Abbrev.: ACR: American College of Rheumatology; AE: Adverse event; DAS28: 28-joint Disease Activity Score; DAS44: 44-joint Disease Activity Score; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; nP: non-Prednisone group; P: Prednisone group; SF-36: 36-Item Short Form Health Survey; SHS: modified Sharp/van der Heijde score; VAS: Visual Analog Scale (Pain)

High-dose prednisone in rheumatoid arthritis

The short-term, high-dose use of prednisone in RA is a very important option in particular in a flare situation. The i.v.-administration as well as the oral application of high(er) prednisone doses provide rapid symptom and pain relieve which is difficult to achieve by any other drug. Effectiveness is therefore beyond debate; more important, a clinical problem and matter of research, is *safety* (see *Table 5*). This also applies for medium to high dosages, though (as drawn out under *Pharmacodynamics*) the effects of prednisone and GCs in general are strongly dose-dependent which unfortunately is also true for side effects.

In the just recently published IMPROVED study, aiming for the most effective treatment strategy in inducing remission in early arthritis [104], every patient (n=610) started treatment with 15 mg of MTX and a high dose of 60 mg prednisone, tapered down within 7 weeks to a low-dose scheme of 7.5 mg to induce early remission (4 months). Remission rate was 61 % with 32 % being in drug-free remission after 1 year. Of the patients not reaching early remission by using the MTX/prednisone-tapering scheme, randomization to adalimumab plus MTX led to more remissions at year 1 than using a DMARD combination therapy consisting of MTX, hydroxychloroquine and sulfasalazine plus prednisone. Though the results demonstrate the effectiveness of the MTX/prednisone-tapering combination (as well as the potential of adalimumab), the study also brought up 14 serious adverse events (including infections, cardiovascular disease, femoral head necrosis), that might be related to prednisone use. Unfortunately, there are no more details on the S(AE)s association to prednisone provided, but it could be assumed that the SAE rate might be resulting from the rather high induction dose, even if tapered down over weeks.

Glucose metabolism

Obviously, RA itself is not only interfering with bone metabolism but also influences glucose metabolism; as a matter of fact, insulin sensitivity decreases with increasing disease activity [96, 105]. In a recent trial by den Uyl et al [105], not even medium to high doses of prednisone, given for one week, did have an impact on glucose tolerance, even if tolerance was previously impaired. Latest data is therefore suggesting that even a short-term medium to high dose of GC is not necessarily impairing glucose tolerance or β-cell function, which is just in line with the evidence outlined for long-term use of low-dose GC above. Due to individual differences in

glucose tolerance and the mentioned assumption of a prednisone therapy possibly worsening a pre-existing impaired glucose tolerance, proper monitoring according to the recommendations is mandatory.

Very High-Dose Use

The very high and pulse-dose use of GC goes along with an increase of the non-genomic effects providing the rapid drug impact since GCRs are completely saturated at daily doses of 100 mg of prednisone and above [34].

A recent meta-analysis of glucocorticoid pulse therapy (≥ 250 mg prednisone equivalent) including 8 trials (4 placebo-controlled, 4 not placebo-controlled) shows a high rate of adverse events of 35/100 patient years, with predominantly cardiovascular AEs being reported [106]. This excellent analysis has its limitations due to the data analysed, e.g. one of the trials only reported short-term AEs while other provide also long-term AEs.

Rates of Adverse events seem to be low to moderate; a meta-analysis from 2009 [78] showing the lowest AE rate (43/100 patient years) among the investigated indications, namely RA, chronic inflammatory bowel diseases (IBD – 555/100 patient years) and polymyalgia rheumatica (PMR – 80/100 patient years). These finding goes along with previous studies [75, 76] as well as the data presented by current clinical trials and different investigations on known prednisone-side effects [79, 81, 88, 89, 96, 105].

With regards to the presented data and the just recently published current EULAR recommendations [83], proper individual risk assessment as well as continuing clinical and laboratory monitoring is vital when prescribing prednisone at medium or high doses. The prescribing physician should always aim for the shortest treatment duration possible. If a prolonged treatment seems clinically necessary, prednisone-sparing agents should be considered and used, if applicable.

TABLE 5. Results of recent clinical trials on various undesired effects of prednisone.

1st author	den Uyl [105]	Engvall [81]	Hoes [96]	Garcia-Gomez [88]	Engvall [79]	Peters [89]
published	2012	2011	2011	2008	2008	2007
category	glucose metabolism	osteoporosis	glucose metabolism	blood lipids	osteoporosis	blood lipids
n	21 vs. 20	50 P vs. 50 nP	82 P- vs. 58 P+ vs. 50 HC	65 P vs. 13 nP	70 P vs. 80 nP	80 (n=35 for P)
special characteristics	none	none	none	all patients female	none	Infliximab
RA diagnosis	< 2 yrs.	8 yrs. median	> 2 yrs.	13 yrs. mean	< 1 year	10 yrs. median
Study duration	1 week	cross-section	1 year	cross-section	2 years	48 weeks
Prednisone dose	60 vs. 30 mg	5-7.5 mg	5-10 mg	2-10 mg	7.5 mg	4.6-8.3 mg median
DMARD & dose	n.a.	n.a.	any	any	any	MTX 15 mg (n=77), Infliximab 3-7.5 mg/kg
remarkable outcome	no deterioration of previously impaired glucose tolerance in neither 30 nor 60 mg	no BMD impairment in Pn group, higher fat mass in Pn group	P- and P+ both had decreased insulin sensitivity and β-cell function compared to HC	HDL increased in P group, other lipid parameters unchanged	femur BMD only decreased in nP group; spine BMD decreased in both groups	reverse association between prednisone doses and atherogenic index (i.e. prednisone led to higher HDL-cholesterol)

Abbrev.: Atherogenic index: total/HDL-cholesterol; HC: Healthy Controls; nP: non-Prednisone group; P: Prednisone group; P-: Prednisone naïve; P+: current prednisone

Conclusion & Expert Commentary

Prednisone and its close relative prednisolone are still representing one of RA therapy's cornerstones.

The biggest advantage of prednisone needs no comment: it has been used over half a century by physicians all over the world and their clinical side effects as well as dosing are well known.

Recent clinical trials revealed a disease-modifying potential of low dose prednisone in early RA, especially in combination with a DMARD such as MTX. Studies showing the induction of a remission as well as the reduction of radiographic joint destruction. Rates of adverse events of prednisone seem to be low to moderate in particular in RA patients.

Taken together, low-dose prednisone therapy can be considered safe as long as the prescribing physician properly evaluates the individual co-morbidities as well as the patient's actual risk for distinct side effects such as osteoporosis or diabetes mellitus. Therapy and dosing decisions should be based on good clinical praxis, laboratory results, disease activity parameters and patient consent.

Higher doses of prednisone seem to be associated with an increased risk of unwanted side effects. Their use should therefore be restricted to unavoidable settings and always be used as long as necessary, but as short as possible. Prednisone-saving agents should be utilised if practicable to reduce both, the daily and cumulative prednisone dose.

The development of modified-release prednisone was a promising milestone in advancing the conventional and well-known drug. With the gained knowledge about the circadian rhythm of cytokine levels in RA, it is possible to reduce the patient's morning stiffness significantly. So far no difference in pharmacokinetics and unwanted side effects could be demonstrated. However, studies are warranted to investigate the development of GC related side effects in the long term for MR prednisone. One can hypothesise that circadian adjusted GC therapy will finally lead to a reduction of side effects. The higher mean treatment costs for MR prednisone are balanced by a possible delay in initiating expensive biological treatments and a recent cost-effectiveness analysis demonstrating positive cost-effectiveness of MR prednisone.

5-year Outlook

Medical science, just like every other science, is always advancing very fast introducing new inventions on a regular basis.

What are the prospects of prednisone in RA therapy? We are talking about a rather old drug being well studied. It is a drug with great potential and it will stay a cornerstone of RA's therapy. In particular when treating arthritis flares there is no potent alternative providing such a fast impact and symptom relieve. Growing evidence implies that prednisone provides DMARD-like potential. However, further investigations, particularly focusing on that topic, are needed to strengthen the role of GC in RA therapy.

As we have outlined above unwanted adverse effects and the unphysiologically timed prednisone application in the morning are the main drawback of GC therapy. Therefore, new developments are necessary to increase effectiveness of GC therapy with possibly decreasing unwanted adverse effects. In this respect, MR prednisone is a step forward enabling the medical community to apply prednisone at the same time when human cortisone levels are peaking. We expect that MR prednisone might catch more attention and probably will find a wider use in clinical medicine.

Furthermore, there are new developments trying to dissociate GC effects mediated by transrepression from effects mediated by transactivation, respectively. Research efforts could identify selective GCR agonists (SEGRAs) being promising developments. The background of this new drug class is the assumption that the immunosuppressive effects of GCs were mainly depending on transrepression [33] as described above, while (metabolic) side effects would basically depend on transactivation. Early investigations have been promising [48], however, the dichotomy has been challenged and it seems to be a simplification of the signalling processes. In animal models it could be demonstrated that this paradigm has to be adjusted since an anti-inflammatory response is not fully detectable while *some* AEs typical for GC administration, e.g. negative impact on bone metabolism were observed [107]. Taken together, transrepression seems to be *mainly* responsible for GC's therapeutic effects while transactivation is probably *rather* mediating adverse effects but also being involved in immunosuppression. A distinct dissociation seems to be difficult to achieve, however, a reduction of unwanted adverse effects is feasible. Just recently the results of a phase II study of a promising SEGRA (PF-04171327 prodrug of PF-0251802) on a small number of RA patients were published

demonstrating a significant better DAS28 reduction compared to prednisone as well as placebo [108, 109]. AEs are reported being mild (predominately headache) warranting further development of this compound.

In conclusion, prednisone will stay a major player in the armamentarium of a rheumatologist treating patients with RA. However, efforts are still necessary to improve effectiveness and to reduce unwanted adverse effects in particular with high doses of prednisone or long-lasting therapy. First developments of new drugs are promising and it is eagerly awaited whether these specifically designed compounds will translate into clinical practice.

Key Issues

- Low-dose prednisone therapy provides DMARD-potential in reducing radiographic joint destruction in RA, particularly in combination with synthetic DMARDs.
- Together with DMARDs remissions can be induced by low-dose prednisone treatment.
- Unwanted adverse effects of low-dose prednisone cannot be neglected, but rather seem to be overestimated. Overall, side effects as well as therapeutic effects are dose-dependent.
- With respect to osteoporosis, low-dose prednisone therapy seems to counteract the negative impact of RA as an inflammatory disease on bone metabolism.
- Higher prednisone doses are associated with more unwanted drug effects. Therefore, medium to high doses should be strictly limited to the clinical needed period of time.
- Modified-release (MR) prednisone improves morning stiffness in RA patients to a meaningful extent.
- Safety and pharmacokinetics of MR prednisone are comparable to conventional prednisone formulations.
- New developments like selective GCR agonists (SEGRAs) might become more important, providing more therapeutic but less side effects.

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